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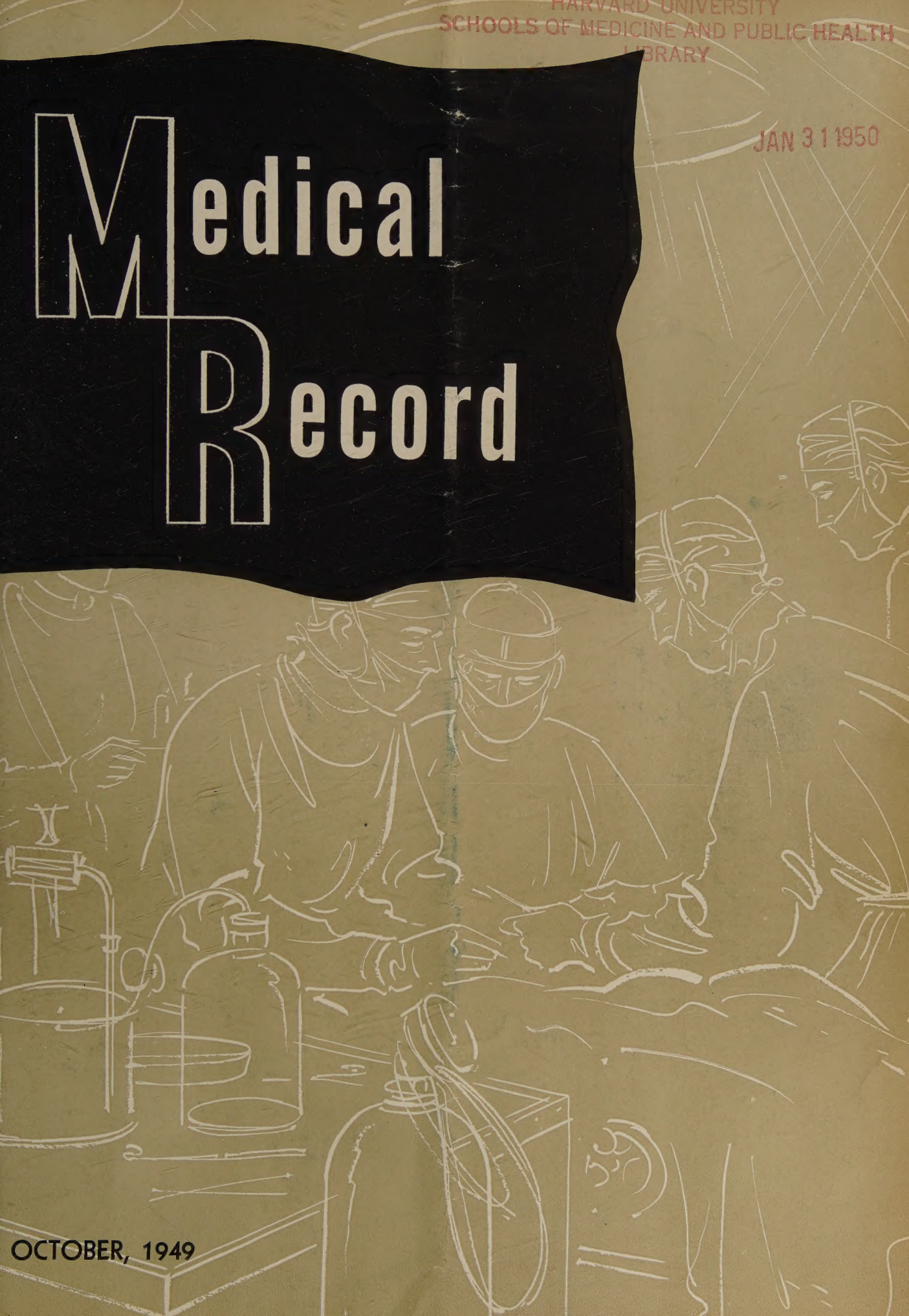

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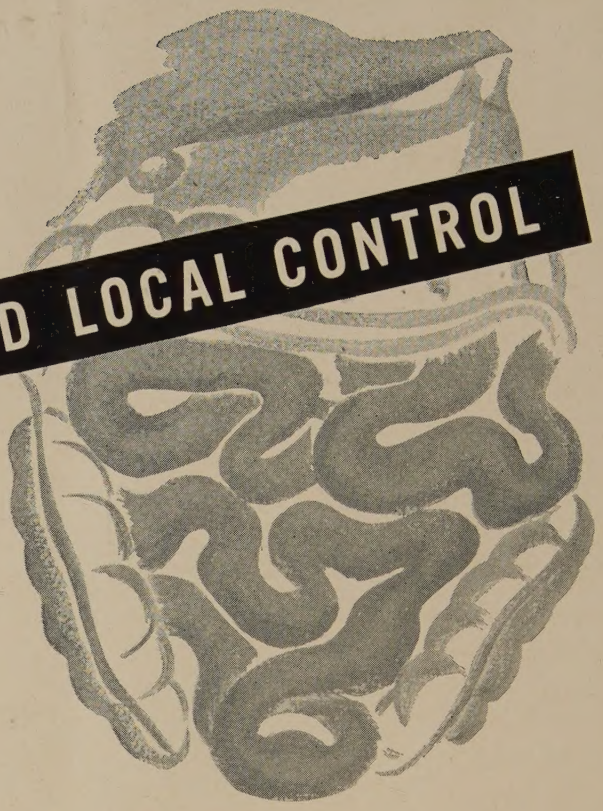

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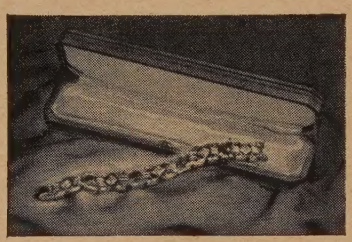

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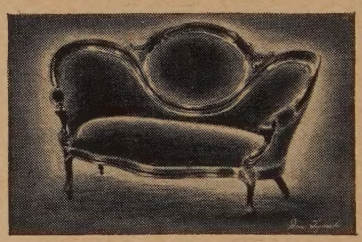

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THE PREGNANCY TOXEMIAS

The Role Of The Trophoblast And The Pancreas

ERNST T. KREBS, JR., San Francisco, Calif*
CLIFFORD L. BARTLETT, M.D., Pasadena, Calif.**

With the single exception of cancer, the pathogenesis of no disease has afforded a more fertile field for sterile speculation than the toxemias of pregnancy. Thereby the pregnancy toxemias — "morning sickness", preeclampsia and eclampsia — have aptly earned their frequent designation as "the disease of theories". It is not without significance that the pathogenesis of cancer and the pathogenesis of the pregnancy toxemias have alike remained inscrutable. Indeed, as we shall observe, the fundamental solution of the one problem is implicit in the solution of the other.

The product of conception, or the conceptus, is the physical basis for the toxemias of pregnancy. This is conclusively demonstrated by the dramatic resolution of the signs and symptoms of pregnancy toxemia following the emptying of the uterus. As we have observed in the study of the life-cycle of antithetic metagenesis (Krebs, 1949), the mammalian product of conception is divisible into two components: (1) the definitive embryo and embryonal membranes and (2) the trophoblast, which is composed of a cellular and syncytial aspect. That the pregnancy toxemias are primarily associated with the trophoblastic aspect of the conceptus is quite clearly demonstrated in the fact that these toxemias will persist in the absence of the definitive embryo and in the sole presence of the trophoblast-containing membrane, the chorion. Indeed, the occurrence of the toxemias of pregnancy in the presence of hydatidiform moles is not uncommon (Revnia & Jamain, 1945; Chesley, Cosgrove & Preece, 1946; Melody, 1946; Ten Berge, 1947; Mueller & Lapp, 1949). Numerous workers have, at one time or another, correctly identified the pregnancy toxemias with the placenta; but most of them have postulated tenuously associated metabolic upsets peculiar to the female as *inextricably* associated with the pathogenesis of toxemia. The necessity for such postulates has been nullified by the fact that in testicular chorionepithelioma in the male all the signs and symptoms of pregnancy toxemia have been described, and these have disappeared dramatically following orchidectomy. In view of these facts, we must at once discard all theoretical detritus that would associate the toxemias of pregnancy with the definitive embryo or with some vague metabolic process supposedly peculiar to the female.

We are thus reduced to a single anatomical variable in the pathogenesis of the pregnancy toxemias: the trophoblast. The trophoblast comprises two morphological and functional elements: (1) the cellular trophoblast or cytotrophoblast and (2) the syncytial trophoblast or plasmoditrophoblast. Since the trophoblast cell is the most primitive cell in the life-cycle, the functional failures it may sustain are relatively few, But a highly primitive cell may show either (1) an over-proliferation or (2) a depression in the proliferation rate.

Of cardinal relevance, then, to the toxemic state is the degree of trophoblast proliferation. Since the trophoblast comprises two phases, the cellular and the syncytial, it would seem essential to determine in which phase there is a deviation from the normal proliferation rate in the presence of toxemia. Tissue culture studies, however, have shown the syncytial trophoblast incapable by itself of proliferation and that it arises as a regressive adaptation of the cellular phase (Friedheim, 1929; Sengupta, 1935). In examining the trophoblast histologically, Wislocki & Bennett

* *John Beard Memorial Foundation, 642 Capp St., San Francisco, Calif.*
** *Medical Consultant Camarillo State Hospital, Camarillo, Calif.*

(1943) were unable to find any mitotic figures in the syncytial trophoblast, which report confirmed numerous other histological studies on the subject as well as corroborating the earlier *in vitro* observations.

Since only the cellular trophoblast is capable of proliferation, it would appear of obvious importance to ascertain whether there is a deficiency or an excess in the proliferation of such cells in the toxemic state. The quantitative estimation of a given cell type within a tissue on the basis of histological cell counts is not practical and at best can provide inaccurate results. Wherever possible, it is preferable to ascertain cellular concentration in metabolic terms; for in most cases we are more concerned with the functional vitality represented by a given cell type rather than with the simple enumeration of the cell in question. The trophoblast cell provides an excellent indicator of functional vitality and cellular concentration in its chief metabolic product: a specific gonadotrophic hormone, commonly designated "chorionic gonadotrophin" but more precisely described as "cytotrophoblastic gonadotrophin". This hormone can be produced only by the trophoblast cell, and its occurrence in the body fluids is a certain indication of the presence of trophoblast in the organism. This fact, incidentally, has a profound significance in fields other than the toxemias.

The proof that the cellular trophoblast is the sole source of cytotrophoblastic gonadotrophin has accumulated over a period of years. The fact is, of course, implicit in the observation that the extent of the overgrowth of cellular trophoblast, as determined grossly and histologically, varies directly with the serum and urinary concentration of chorionic gonadotrophin to the extent that both diagnosis and prognosis of such overgrowth are based on the determination of serum and urine titers of the hormone. The origin of cytotrophoblastic gonadotrophin has, however, been conclusively demonstrated by tissue culture studies that have consistently displayed a vigorous proliferation of the cellular elements of the trophoblast and a deficiency and final disappearance of the syncytial elements, concomitant with proportionately increasing levels of chorionic gonadotrophin and proportionately decreasing titers of progesterone and estrogen, the latter of which disappeared from the tissue cultures with the disappearance of the syncytial trophoblast (Nagayama, 1937, 1938; Gey, Segar & Hellman, 1938, Jones, Gey & Gey, 1943; Stewart, Sano & Montgomery, 1948).

It is clear that chorionic gonadotrophin is produced by the cellular trophoblast, cytotrophoblast or Langhans cells; and that the syncytial trophoblast or plasmoditrophoblast produces the sex steroids of the placenta. Because the syncytial trophoblast arises from the cellular trophoblast, it is evident that the normally occurring factors *in vivo* that induce such syncytial adaptation are missing *in vitro,* which deficiency in the tissue culture medium not only accounts for the absence of the syncytial phase of the trophoblast but also for the relative increase of the cellular and plastic; it is acted upon by tissue and humoral factors. It is not capable itself of differentiation. The origin of its syncytial exhibition shares a mechanism phase. The trophoblast *morphologically* is passive common to primitive syncytial formation; this mechanism is primarily a protective one. In the presence of antithetic forces, a syncytium presents a greatly reduced vulnerability through virtue of a spectacular increase in the ratio of nuclear and cytoplasmic elements to the reactive and highly vulnerable surface area of *cellular* membranes. Within the gravid organism this adaptation is well integrated with the endocrine needs of gestation; therefore, in human gestation, for example, we find an highly elevated titer of chorionic gonadotrophin in the blood and urine during the first trimester. The peak of the excretion curve of chorionic gonadotrophin in human pregnancy is reached around the 56th day of the span of gestation. After this period there is a precipitous drop in the excretion curve for chorionic gonadotrophin and a reciprocal rise in the excretion curve for the syncytial steroids, estrogen and progesterone (Fig. 1). Curiously enough, this alteration occurs concomitantly with the commencing function of the foetal pancreas.

Paralleling the high titer of chorionic gonadotrophin in the first half of the first trimester and the relatively high titer of sex steroids in the later two and one-half trimesters, are the concentrations of cellular and syncytial trophoblast, respectively. In the commencement of the span of gestation, the highly luteinizing chorionic gonadotrophin of the cellular trophoblast acts to insure the integrity of the corpus luteum in its production of progesterone and estrone, by which the progravid phase of the uterus is maintained and uninterruptedly passed to the gravid phase. This action prevents the withdrawal of ovarian steroids from the uterus, which withdrawal would physiologically precipitate the menstrual breakdown of the uterine endometrium. It is thus obvious that the cellular trophoblast acts as a substitute anterior pituitary in extending the function commenced by the luteinizing hormone of the anterior lobe of that gland in the ovarian cycle. The human conceptus, however, is protected by a double endocrine assurance, as it were. Bilateral oophorectomy even very early in human gestation will not, as a rule, result in abortion, since the syncytial phase of the trophoblast produces a sufficient quantity of ovarian-like steroids to maintain the integrity of the gravid uterus.

We have already noted that the single variable in the pregnancy toxemias is the presence of trophoblast tissue. The next consideration is whether there is an overgrowth or a deficiency in such trophoblast and the manner in which either accounts for the toxemias of pregnancy.

The toxemias of pregnancy are uniformly characterized by an overgrowth of cellular trophoblast with a consequent deficiency in syncytial trophoblast. Excessive chorionic (cytotrophoblastic) gonadotrophin in the blood and urine of patients with toxemia was first reported by Smith & Smith (1933, 1934, 1935), who demonstrated also that the placentae of toxemic patients contained more gonadotrophin than could be recovered from those of normal pregnancy and that the high gonadotrophic titer of blood and placenta in toxemia was not accountable to pituitary gonado-

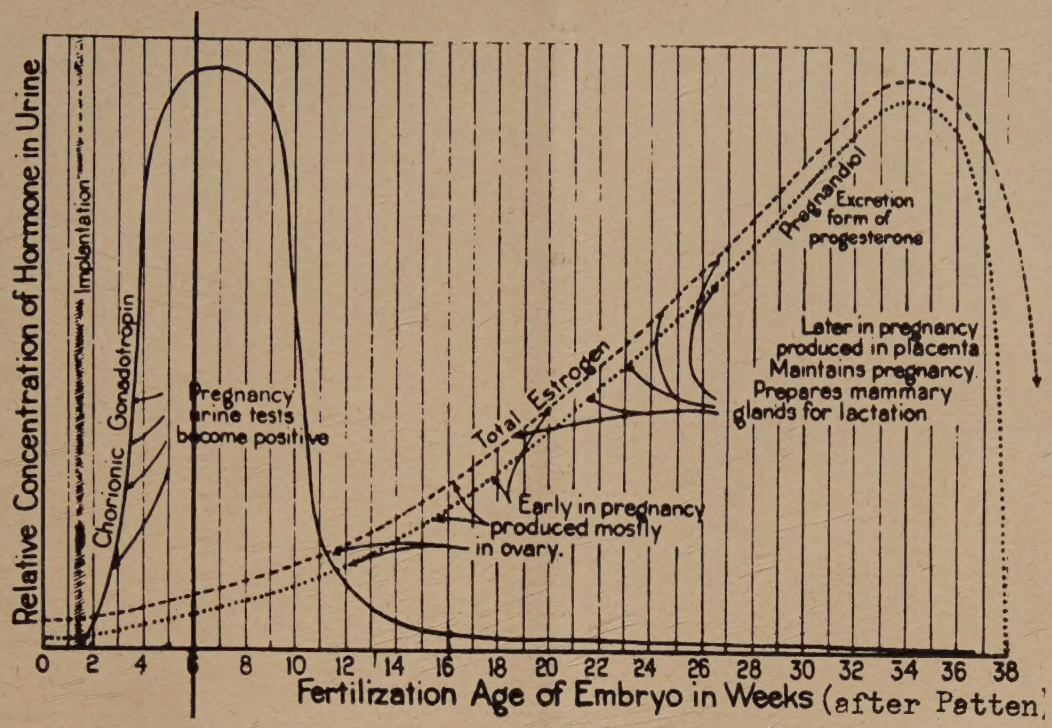

FIG 1.

Chorionic gonadotrophin is produced by the cellular trophoblast; the total estrogens, chiefly by the syncytial trophoblast. Commencing function of the foetal pancreas is concomitant with the fall of the excretion curve for gonadotrophin and wtih the reciprocal rise of the curve for the syncytial steroids. In the pregnancy toxemias hydatidiform moles, or chorionepithelioma there is a progressive failure in the fall of the gonadotrophin excretion curve and in the rise of the total estrogen curve (cf. text).

trophin (Smith & Smith, 1935). The abnormally high concentration of chorionic gonadotrophin in the blood and urine of toxemic patients was confirmed by numerous workers (Heim, 1934; Bourg & Le Grand, 1935; Anselmino & Hoffman, 1936; Tenney & Parker, 1937; Rakoff, 1939; Siegler, 1939; Watts & Adair, 1943). Since chorionic gonadotrophin is the specific product of the trophoblast cell, a pronounced elevation in the production of this hormone means a corresponding increase in the functional vitality and/or number of trophoblast *cells.*

We have observed from tissue culture studies of trophoblast that the syncytial trophoblast is the regressive adaptation of the cellular trophoblast and that it will not divide. It is also the exclusive trophoblastic source of progesterone and estrone. The syncytial trophoblast arises in response to an *in vivo* antithesis to the trophoblast; and, this antithesis being absent in tissue culture, the cellular phase of the trophoblast is free to proliferate in an unchecked fashion with a consequent diminution and final disappearance of the steroid-producing syncytium. In the toxemias of pregnancy, then, the question arises whether the overgrowth of cytotrophoblast — as reflected in the elevated c.g.h. titers — is the result of a stimulus intrinsic to proliferation within the trophoblast cell, or the result of the absence of restraints normally acting against the trophoblast cell. If it is the former, then we can expect an increased concentration of cellular trophoblast or cytotrophoblast to be accompanied by a corresponding increase in the concentration of syncytial trophoblast; and, if it is the latter, we may expect a radically asymmetrical concentration of cytotrophoblast with a correlatively pronounced deficiency in syncytial trophoblast. In the first case there should be an excess in *both* chorionic gonadotrophin and the syncytial steroids (progesterone and estrone); and, in the latter, there should be an abnormal increase in c.g.h. with a corresponding deficiency in syncytial steroids.

The toxemias of pregnancy are characterized by an abnormally high excretion of chorionic gonadotrophin and a deficient excretion of the syncytial steroids. In 1938 three groups of investigators, working independently, reported low values for the urinary product of the syncytial steroids (Browne, Henry & Venning; Smith & Smith; Weil). These findings have been well confirmed (Taylor & Scadron, 1939; Smith & Smith, 1940; 1941; Bachman, Leekley & Hirschmann, 1941; Bachman, Leekley & Winter, 1941).

What is the factor the deficiency of which accounts for the unchecked overgrowth of the cellular trophoblast and the consequent deficiency in the syncytial aspect of the trophoblast? The responsible factor is, perhaps, adumbrated in a fact that we have earlier mentioned: that the degeneration in the growth of the

cellular trophoblast and the increase in syncytial trophoblast are concomitant with the commencing function of the foetal pancreas. This principle was first defined by John Beard, of the University of Edinburgh, who observed a concomitance between the degeneration of the cellular trophoblast and the commencing function of the foetal pancreas. In his classical memoirs on the subject, he described this concomitance not only for vertebrates and their trophoblast, but for invertebrates and their trophoblastic homologues, as well. With such precision were these studies accomplished by Beard that fifty years ago he described, almost to the day, the average time at which the human pregnancy trophoblast (based on commencing function of the foetal pancreas) would undergo "cataclysmic degeneration". After the elapse of almost fifty years and with the subsequent discovery of the trophoblast-cell-produced chorionic gonadotrophin, Patten (1946) compiled a composite excretion curve for c.g.h. throughout the span of human gestation. Only the data of numerous workers could afford a statistically precise curve. Reading on the abscissa of the graph, depicting the excretion curve of c.g.h., in the 280-day span of human gestation, we find that a line drawn vertically to the day which Beard described as marking the concomitance between foetal pancreas function and trophoblast degeneration, will bisect the peak of the excretion curve for c.g.h. (Fig. 1). This not only illustrates the accuracy with which this original work was done, but it further confirms the association between c.g.h. excretion and the growth of the cytotrophoblast.

The fact of an association between foetal and maternal pancreatic function and the growth of the trophoblast, of course, does not necessarily exclude the remote possibility of an accessory mechanism to account for some pregnancy toxemia. Indeed, in the valid concomitance between commencing foetal pancreatic function and trophoblast degeneration, we must be conscious of a possible logical fallacy: concomitant concurrence does not *always* prove a causal relationship. It is necessary for us to seek further observational and experimental evidence for an association between the overgrowth of trophoblast cells and the deficient function of the foetal and/or maternal pancreas.

To establish an association between pancreatic deficiency and the overgrowth of the cellular trophoblast, on the one hand, and the toxemias of pregnancy, on the other, it is necessary to determine the effect of the functional impairment of the pancreas on the incidence of pregnancy toxemia and the correlatively abnormal excretion of c.g.h. Diabetes is, of course, the classical example of an expression of pancreatic insufficiency; in this disease the pancreas gland is deficient frequently in both its endocrine and exocrine function. *It is noteworthy, therefore, that diabetes is the only disease which we know that is consistently associated with a greatly increased incidence of pregnancy toxemias* (White, 1935; Dieckmann, 1941; Lavietes, Leary, Winkler, & Peters, 1943; Bill & Posey, 1944; Gaspar, 1945). Smith & Smith (1948) point out that the significance of the very high incidence of toxemias in diabetic women who are pregnant has not yet been elucidated.

That the toxemia in pregnant diabetics is directly associated with the overgrowth of the cellular trophoblast is suggested by the fact that not only are the toxemias of pregnancy in diabetic women associated with an abnormally high excretion of chorionic gonadotrophin, but that the elevation in c.g.h. in diabetes complicating pregnancy has excellent prognostic value for the subsequent development of a clinical toxemia (White, Titus, Joslin & Hunt, 1939; White & Hunt, 1940; White, 1945). White observed that an abnormally high serum titer of c.g.h. was invariably followed by clinical pathology and that the gonadotrophin was consistently low in uncomplicated pregnancy in diabetic women. Her findings were confirmed by the Smiths (1937, 1938, 1939).

Not only is there a high correlation between the incidence of diabetes and the toxemias of pregnancy, but there is also, specifically, a direct correlation between the incidence and degree of toxemia in pregnant diabetics and the incidence of abnormally high gonadotrophin levels. In a series of pregnant diabetics White (1947) found that 65 per cent either spontaneously aborted or developed pre-eclampsia, but in those diabetics exhibiting a normal titer for chorionic gonadotrophin and the syncytial steroids, the fetal survival was 97 per cent, the incidence of pre-eclampsia was 2 per cent, and that of premature deliveries, zero. Mueller (1947) made similar observations in female rabbits rendered diabetic by alloxan injections.

Since an abnormally high titer of c.g.h. and an abnormally low titer of syncytial steroids were observed by White et al in 75 per cent of the pregnancies complicating diabetes, it would appear that the responsible factor in the pancreas gland in these cases is not insulin, but some other pancreatic factor or factors whose deficiency is frequently a concomitant of endocrine deficiency responsible for diabetes. That insulin plays no direct role in the phenomenon is proved by the demonstration that injections of this hormone have no effect whatever either upon the hormone titers or the degree of toxemia. We will, however, recall that the commencing function of the foetal pancreas, which is concomitant with the rapid degeneration of the trophoblast or its phylogenetic homologue, is evinced by the appearance of zymogen granules in the gland. These granules are, of course, the source for the exocrine secretions of the pancreas, the pancreatic enzymes. It is also appreciated that a deficiency in the production of these enzymes *usually* accompanies the pancreatic deficiency that characterizes diabetes. Indeed, it is infrequent that an organ is strongly deficient in one function and completely normal in another.

The pancreatic enzymes possess a very specific action on the cellular trophoblast and are capable of *selectively* digesting chorionic gonadotrophin and the cell which produces it. Consideration of this aspect of the subject will be deferred for the moment.

The role of the non-insulin factor in the pancreatic dysfunction associated with the pregnancy toxemias is illustrated by the fact that the incidence of stillbirths and neontal deaths *is very high for several years before clinical evidence of diabetes is found* (Allen, 1939; Miller, Hurwitz & Kinder, 1944; Miller, 1945).

This high fetal and neontal mortality in mothers disposed to diabetes but not yet insulin-deficient. has further been related to a pathological excess in c.g.h. and a deficiency in the syncytial steroids (White & Hunt, 1943; Smith, Smith & Hurwitz, 1944; Rubin, Dorfman & Miller, 1946).

The toxemias of pregnancy are thus characterized by: (1) an overgrowth of cellular trophoblast, (2) an undergrowth of syncytial trophoblast, (3) excessive production of chorionic (cytotrophoblastic) gonadotrophin, (4) deficient production of syncytial steroids, (5) a non-insulin pancreatic insufficiency, and (6) a total refractoriness to insulin therapy.

Therapy of Pregnancy Toxemias

The hormonal imbalance that characterizes the toxemias of pregnancy immediately suggests two fundamental therapeutic measures: (1) the correction of the deficit in syncytial steroids (sometimes miscalled "ovarian steroids"), and (2) the ablation of the excessive production of chorionic gonadotrophin produced by the trophoblast cell, with the restoration of a normal hormone balance. The first approach has been empirically utilized with a high degree of success during the past decade. Priscilla White, one of the pioneers and more able students of substitutional hormonal therapy, found that the administration of estrogen to pregnant diabetics increased foetal survival, from a level ranging between 40 and 60 per cent to a level of 90 per cent. Spontaneous abortion and pre-eclampsia, following steroid therapy, dropped from 40 per cent and 25 per cent, respectively, to 5 per cent for both conditions.

It is interesting to note that substitutional hormonal therapy in pregnancy toxemias is accompanied not only by the correction of the syncytial steroid deficit, but administered estrogen and progesterone act to check the proliferation and activity of the gonadotrophin-producing cellular trophoblast, and thereby depress the chorionic gonadotrophin titer to the normal range. This phenomenon is illustrative of the reciprocal relationship that exists between the cellular trophoblast and its gonadotrophin and the syncytial trophoblast and its steroids. This relationship parallels that existing between the gonads with their steroids and the anterior pituitary with its gonadotrophin. Thus is apparent the appropriateness of our designation of the cellular trophoblast as a "substitute pituitary" and the syncytial trophoblast as a "substitute ovary or gonad".

The rationale of the use of sex steroids in threatened abortion is implicit in the fact that the progestational, as well as the gestational, integrity of the uterus is maintained by the ovarian and syncytial steroids, respectively. Withdrawal of such steroidal support from the progestational uterus will precipitate menstruation; withdrawal of the same support from the gestational uterus will precipitate spontaneous abortion or birth, depending upon whether the withdrawal is pathological or physiological. Indeed, birth may be considered fundamentally as an epimenstrual phenomenon resulting from the ultimate withdrawal of steroid hormonal support from the gravid uterus, as a result of the ablation of the hormone-producing trophoblast, especially the syncytial phase. The foetus of a toxemic pregnancy in some cases is retained for a considerable period beyond the normal date of delivery; this retention is accompanied by a persistence of trophoblastic hormones in the blood and urine. Such hormonal persistence is due to an incomplete destruction of the pregnancy trophoblast by the factor or factors normally responsible for such destruction. Toxemic pregnancies are also characterized by an high incidence of spontaneous abortion. The seeming contradiction between a tendency toward spontaneous abortion and delayed delivery is resolved in the fact that the progesterone-like and estrone-like steroids produced by the syncytial trophoblast are deficient early in pregnancy toxemia not by *virtue of an excessive destruction of syncytial trophoblast but through an inadequate destruction of the cellular trophoblast, in which process it normally undergoes the syncytial adaptation that characterizes normal trophoblast in the last two trimesters of normal human gestation.* Thus, insufficient destruction or checking of cytotrophoblast in the earlier period of gestation may lead to spontaneous abortion through a deficit of syncytial steroids, while the same process in the latter stages of gestation will afford a sufficient excess of trophoblast to provide the hormonal support responsible for the extension of the span of gestation in the pregnancy toxemias.

The syncytial aspect of the trophoblast in the pregnancy toxemias has been the source for considerable confusion. The diminution of the syncytial trophoblast of the placenta in toxemias has been the subject of repeated observation by numerous workers. Tenney (1936) was among the first to describe the diminution in syncytial trophoblast as "syncytial degeneration". Later Tenney & Parker (1940) correlated the extent of syncytial diminution in 100 placentae of pregnancy toxemia with the severity of the disease, and they concluded that "placental damage begins before clinical signs of the condition appear". In this report they again designated the diminution as *degeneration.* Wislocki & Dempsey (1946) confirmed these findings in two toxemic placentae and pointed out that the syncytial "degeneration" in such placentae at the fifth month was typical of the normal organ at term. Boyd (1944) is among those who perpetuate the semantic error of describing the diminished syncytial trophoblast as comprising degeneration and premature aging of the villi. From the established morphogenesis of the trophoblast, which ascribes the origin of the syncytial trophoblast to the cellular trophoblast, the logical fallacy in describing the offspring of the cellular trophoblast as "degenerate" or "aged" while faced with an excess of exuberant and young parent cells must be apparent. Indeed, this probably semantically inspired rather than conscious error was for a considerable time a source of confusion to Krebs, who detected the relevance of the pancreatic secretions to the problem of pregnancy toxemias; but because of the erroneous concept of a prematurely aged or degenerated syncytial trophoblast was at first falsely led to consider the possibility that the toxemic process was associated with an excess, rather than an actual deficiency, of the factors of the pancreas responsible for the destruction of the trophoblast. The state of the syncytial

trophoblast in the pregnancy toxemias is preferably described as one of a *syncytial deficit,* rather than as one of syncytial degeneration. It is true that the end morphological result of a *syncytial deficit* is precisely the same as that expressed by true *syncytial degeneration,* but the means by which the former was achieved involved a pathologically inadequate conversion of the cytotrophoblast to the syncytial state, while the latter was achieved by the physiological degeneration of syncytial trophoblast that had undergone normal conversion from the cellular to the syncytial state, in response to the quantitatively normal effect of the agent responsible for such conversion. The continued action of this factor, then, is responsible for the *degeneration of the syncytial trophoblast* recently converted from the cellular stage. A deficiency in this factor is responsible for the *syncytial deficit* involved in the failure of the cytotrophoblast to assume, at the maternal interface, an adequate syncytial adaptation.

We are not here concerned with the clinical practicability of substitutional hormonal therapy: we are concerned only with its biological rationale. We have reviewed briefly the correction of the syncytial hormonal deficit through the administration of estrogen and progesterone. Despite the earlier opinions of some authors, the use of such steroids can not stimulate the syncytial trophoblast to functional activity since, as we have seen, the syncytial trophoblast is incapable of division. Whether such steroid therapy, in depressing the growth and activity of the cellular trophoblast — as reflected in a pronounced depression in c.g.h. production — causes it, in part, to respond to a syncytial adaptation, has not yet been established. The physiology of the trophoblast, however, makes such an adaptation quite tenable.

Beside correcting the syncytial deficit of steroid hormones, the next means of restoring a normal hormonal balance would necessarily involve acting directly upon the trophoblast by an antithetic factor which would, in diminishing the concentration of gonadotrophin-producing trophoblast cells, cause the cytotrophoblast, temporarily at least, to undergo syncytial adaptation and thereby at once depress the abnormally high titer of cytotrophoblastic gonadotrophin and elevate the abnormally depressed titer of syncytial steroids. We have observed that the factor normally responsible for the conversion of cytotrophoblast to syncytial trophoblast and thereby, for the maintenance of a normal hormonal relationship, is almost invariably absent in diabetics who are pregnant; yet, this factor has been shown to have nothing to do with insulin.

What are the probable factors in the pancreas responsible for checking the growth of the cytotrophoblast, causing its gradual adaptation to a syncytial state, thereby diminishing the chorionic gonadotrophin titer and increasing the syncytial steroid titer, and then ultimately destroying the residual syncytial trophoblast and thereby resulting in the ablation of all trophoblast and trophoblastic hormones with the resultant induction of birth? Insulin is not the factor. There remain among the known pancreatic factors, the pancreatic enzymes: chymotrypsin, amylase, carboxypeptidase, trypsin, ribonuclease, and others. In what manner could any of these participate in the destruction of trophoblast? Destruction of trophoblastic protein would, of course, first involve a proteolytic enzyme. Such an enzyme of necessity would have to be an extracellular one, produced by one tissue or organ of the body and transported by the blood to the trophoblast. The pancreas gland is the source of several extracellular proteolytic enzymes. But in order for such proteases to act against the trophoblast cell *in vivo* several things are essential: (1) the proteolytic enzyme must be capable of acting against the trophoblastic protein in a concentration that is non-toxic to the living organism, at a pH the same as the blood and at the temperature of the body; and (2) such a proteolytic enzyme must also be capable of a specific or selective action against the chief protein of the trophoblast cell. The chief protein of the cellular trophoblast is, of course, chorionic gonadotrophin. This is a glucoprotein characterized by the presence of a prosthetic group in which the specific carbohydrate is galactose, which sugar forms a glucosidic linkage with the purely protein aspect of the gonadotrophin moiety.

The two chief proteases of the pancreas gland are trypsin and chymotrypsin. Trypsin is too toxic for parenteral use. Crystalline chymotrypsin, however, has proved non-toxic in man when injected in doses as high as 500 milligrams intravenously within the course of one-half hour.* Since the total blood volume in man comprises about 6,000 c.c., the concentration of chymotrypsin produced in the blood by 500 milligrams is roughly equivalent to a 1: 12,000 dilution. In terms of enzyme action, this is a very concentrated solution of enzyme.

The only enzyme of the pancreas capable of acting upon carbohydrates is crystalline amylase. That pancreatic amylase is relatively non-toxic is implicit in the fact that *normal* plasma contains between 80 and 150 units (Somogyi method) of pancreatic amylase, while normal urine contains from 3 to 30 units of amylase (Wohlgemuth's method). The fact that this amylase is of pancreatic origin is proved in the elevation of urinary amylase to as high as 100 or more units in acute pancreatitis, with a similar elevation in the plasma amylase level.

Since both crystalline chymotrypsin and crystalline pancreatic amylase are readily tolerable in enzymatically effective levels in the human blood plasma, the next question that arises is that of their selectivity or specificity of action against the chief protein of the cellular trophoblast. *It is obvious that in order for these enzymes to be non-toxic toward the somatic tissue of the host within which they act, these enzymes must have no effect upon living somatic cells of the host.* In this respect their action must, indeed, *be very efficiently inhibited.* The efficiency of such inhibition is a corollary of their non-toxicity.*

* Tagnon, Weinglass & Goodpasture (1945) determined the intravenous lethal dose of chymotrypsin in dogs to be between 40 and 60 mgs per kg of body weight. This is between 140 and 210 times the intramuscular dose used in human therapy. Since the material used by the Harvard workers was admittedly impure, more recent findings by others have indicated a lower order of toxicity for the enzyme in mammals. It must be emphasized, however, that, like all other proteins, chymotrypsin presents the problem of antigenicity in some subjects. This is readily met by commonplace clinical precautions.

In comparing the specificity of crystalline chymotrypsin and crystalline amylse against the distinctive protein of the cellular trophoblast, chorionic gonadotrophin, it is obviously necessary to use a somatic* protein as a standard. For this purpose we should choose from the soma a protein that is most nearly related to chorionic gonadotrophin. Anterior pituitary gonadotrophin is such a protein. Thus, if there is any overlapping in specificity between the trophoblast gonadotrophin and somatic proteins, this overlapping must be expected to occur with anterior pituitary gonadotrophin.

In 1939 Abramowitz & Hisaw reported that while crystalline chymotrypsin failed to inactivate anterior pituitary gonadotrophin *in vitro,* this enzyme completely inactivated chorionic gonadotrophin under the same conditions. They also found that while the gonadotrophin of the anterior pituitary was not inactivated in its luteinizing effect by preparations of *crude* salivary amylase, chorionic gonadotrophin was inactivated under the some conditions. Though crystalline pancreatic carboxypeptidase failed to inactivate anterior pituitary gonadotrophin (Chow, Greep & Van Dyke, 1939) *in vitro,* the same pancreatic enzyme did inactivate the gonadotrophin in the serum of pregnant mares (Evans & Hauschildt, 1942). Moreover, crystalline pancreatic carboxypeptidase and chymotrypsin, as well as amylase, were found by the latter authors to inactivate completely the pregnancy gonadotrophin of mare serum in an *in vitro* concentration that failed to inactivate the same quantity of anterior pituitary gonadotrophin.

That crystalline chymotrypsin and amylase† have a selective digestive action on chorionic gonadotrophin, there is no doubt. The *in vitro* studies performed to date indicate a high degree of selectivity on the part of chymotrypsin and amylase against chorionic gonadotrophin, as compared with a relative inertness toward anterior pituitary gonadotrophin. The specificity of these reactions will be bronght into much sharper focus when the enzyme concentrations employed for the *in vitro* work are expressed in terms of the minimum concentration necessary, in the minimum time, to digest chorionic gonadotrophin under standard temperatures and pH. The use of *crystalline* pancreatic amylase will also sharpen the specificity of the amylase reaction against chorionic gonadotrophin. Indeed, it is quite impressive to find in tissue culture work that the *specificities* of these pancreatic enzymes toward chorionic gonadotrophin persist in the presence of inordinately high enzyme concentrations, acting over 24 hours or more, as compared to the immunity of the anterior pituitary gonadotrophin under the same conditions. As is a commonplace in enzyme dynamics, crystalline proteolytic enzymes will digest any protein if given adequate time in the presence of a sufficiently high enzyme concentration at an optimum temperature and pH. Specificity or selectivity appears for such enzymes only at the lower levels of enzyme concentration. Thus it is, indeed, surprising to find the enzyme specificities toward chorionic gonadotrophin persisting over rather wide ranges. Such persistence suggests a substantial biological basis.

Crystalline chymotrypsin, crystalline carboxypeptidase and crystalline pancreatic amylase will selectively digest chorionic gonadotrophin in concentrations and at the pH and temperature tolerable to the host. The second means, then, of correcting the hormonal imbalance that comprises the pregnancy toxemias is to employ the specific enzymes of the pancreas that will selectivity destroy chorionic gonadotrophin, the distinctive protein of the cellular trophoblast, and that will thereby induce the synctial adaptation of cytotrophoblast, with the resultant correction of the deficit in syncytial steroids.

Crystalline amylase exhibits an especially marked specificity toward cytotrophoblastic gonadotrophin. This enzyme is found in normal blood and urine in the active form over a wide range of concentrations. It is especially indicated in the toxemias of pregnant diabetics because (1) the foetal pancreas does not produce amylase, which production does not commence until some time after birth, and (2) in the presence of diabetes the maternal pancreas gland is deficient in amylase. In fact, the diminution in the enzymic activity of the pancreas in human diabetics has been the subject of considerable study (Jones, Castle, Mulholland & Bailey, 1925; Gavrila & Paraschivesco, 1926; Babkin, 1935; Huggins & Russell, 1948; serum deficiency in amylase in diabetics). And in the dog Iazo & Dobreff (1925) observed a small but definite increase in the enzymic secretion of the pancreas gland after the administration of insulin. These data bear out the generalization that a marked deficiency in the function of one aspect of an organ or tissue is usually accompanied by some degree of depression in the function of other aspects of the tissue or organ. In the case of insulin and the pancreatic enzymes other than amylase, an insufficiency in the function of the maternal pancreas may be compensated by an increase in the efficiency of foetal pancreatic function. Thus it is a clinical commonplace to find pregnant diabetics supported in part by the insulin of the foetal pancreas. Indeed, it is not unknown for the infants of such mothers to go into insulin shock immediately after birth, because of the compensatory hyperinsulinism induced by the prenatal environment of a diabetic mother.

Because there is in the presence of pancreatic dysfunction in the pregnant woman an uncompensated decrease in pancreatic amylase, there must be expected a corresponding deficiency in the degradation of the prosthetic carbohydrate linkage in the chorionic gonadotrophin protein. This is partly reflected in an abnormally high gonadotrophin titer with the corresponding overgrowth of cellular trophoblast, which overgrowth contributes to the alteration of the membrane that separates the mother from the conceptus. This alteration in the critical semi-

* We employ the appelation *somatic* to describe all the elements belonging to the body of the individual. Since the trophoblast comprises tissue belonging to the life-cycle of the conceptus — and not of the body of the individual in which it happens to be harbored — the trophoblast is *non-somatic.* This distinction, and the biological grounds for it, is fully reviewed in the chapter on "Antithetic Metagenesis" in "The Biological Basis of Cancer". (In press).

† Enzymes supplied through courtesy of Spicer Gerhart Co., Pasadena, Calif.

permeable membrane in gestation contributes to the toxemia complex.

There are, however, in the presence of maternal pancreatic dysfunction — despite the absence of amylase in the foetal pancreas — the enzymes of the foetal pancreas. These enzymes, as we have observed, are capable of selectively destroying the chief protein of the trophoblast cell. As a result, the absence of amylase is not so critical as it otherwise would be. If we study the titers of chorionic gonadotrophin in the blood and urine of pregnant diabetics and in the toxemias in others, we find that although the titer of gonadotrophic hormone may be very abnormal in its elevation — hence in the overgrowth of cellular trophoblast — it never reaches the dramatically high levels that are specifically diagnostic for chorionepithelioma, nor does it often reach the levels found in most hydatid moles. It is only when the definitive embryo or foetus is withdrawn from the trophoblast, through spontaneous abortion or retained placenta, that the trophoblast cells proliferate to a sufficient extent to produce the hormone titers that characterize hydatid moles and chorionepitheliomas, *which do not occur in the presence of a viable embryo with a functioning pancreatic gland.*

It is appreciated that the stimulus to overgrowth of the cellular trophoblast is not intrinsic to the trophoblast cell, but follows from the ablation of growth restraints that normally obtain *in vivo*. Tissue culture studies have conclusively proved this. It is observed that the pregnancy toxemias are accompanied by an overgrowth, to a degree, of cellular trophoblast, with a corresponding deficiency in the conversion to the steroid-producing syncytial trophoblast and with a corresponding excess of chorionic gonadotrophin in the body fluids. The overgrowth of such cellular trophoblast *in the presence of an embryo* is limited. In the absence of the definitive embryo, the trophoblast may overgrow further to exhibit a hydatidiform mole. In fact, such moles are not infrequently the source for the typical signs and symptoms of the pregnancy toxemias.

Histologically, there is a direct correlation between the concentration of cellular trophoblast, as compared to syncytial trophoblast, in the mole, and the excretion of chorionic gonadotrophin. The cellular trophoblast in the pregnancy toxemias is characterized by an overgrowth; in hydatidiform moles, by even a greater overgrowth; and, in chorionepithelioma, by still a greater overgrowth. The cells involved in all three phenomena are the same. The only difference is in the degree of proliferation. This is demonstrated in the fact that the same chorionic gonadotrophin is found in all three conditions, but that its titer is progressively higher from normal pregnancy to the pregnancy toxemias, from the toxemias to hydatidiform moles, and from the moles to frank chorionepithelioma. Hydatidiform moles are not uncommon; they occur in one out of every 2500 to 3000 pregnancies. An innocent mole is characterized by a very low concentration of cellular trophoblast and a relatively high concentration of syncytial trophoblast. It has been estimated that about 15 per cent of all hydatidiform moles terminate in chorionepithelioma and that one-third or more of all chorionepitheliomas are preceded by a hydatidiform mole. Most hydatidiform moles are associated with a preceding pathological pregnancy; and chorionepithelioma practically never arises following an apparently *normal* pregnancy. *The diagnostic index of all these consists of the correlation of the chorionic gonadotrophin titer of the blood or urine with the time in the span of gestation or postpartum.*

It is, indeed, of perhaps more than casual significance that the excessive proliferation of cellular trophoblast that characterizes the toxemias of pregnancy may so increase in quantity, *without any functional or morphological change whatever in the responsible trophoblast cell,* as to terminate with the exhibition of the *unchanged trophoblast* in the most malignant of all exhibitions of cancer: chorionepithelioma. Let us note that it is quite impossible for the abnormal proliferation of cellular trophoblast that characterizes pregnant diabetics to proliferate beyond a certain range, or produce more than a certain abnormally high titer of chorionic gonadotrophin, without the process inevitably being exhibited as the fiercely malignant chorionepithelioma. In other words, if the pancreatic enzymes that are clearly proved to destroy the chief protein of the trophoblast cell — chymotrypsin, crystalline amylase and carboxypeptidase — act against the chorionic gonadotrophin protein effectively, as they have been proved to do, then they will clearly act to avert the most malignant of all exhibitions of cancer. This subject is treated more comprehensively elsewhere..

It will be appreciated that we have followed the current practice of including the various clinical manifestations of pregnancy toxemia — morning sickness, pre-eclampsia, hyperemesis gravidarum, and eclampsia — within a single class. Despite their somewhat varying clinical manifestations, this is justified since they all share a fundamental pathogenesis. Etiologically they are all cut from the same piece of cloth. That cloth is woven on the loom of the pancreas gland: the warp, the pancreatic enzymes; the woof, the inhibitors of these enzymes.

Despite the fact that the foetal pancreas produces no amylase, this enzyme is found both in the circulation of the foetus and the amniotic liquor (Maeda, 1924). In the rabbit Wohlgemuth & Masson (1912) found the relative concentrations of amylase in pregnancy as follows:

Maternal blood	80
Foetal blood	20
Amniotic liquor	20

The maternal origin of the amylase, despite the uniformity in concentration of the enzyme in the foetus and the amniotic liquor normally, was further demonstrated when these workers ligated the maternal pancreatic duct; this greatly raised the maternal blood amylase; no change occurred in the foetal blood, but a large change occurred in the amniotic liquor:

Maternal blood	320
Foetal blood	20
Amniotic liquor	80

The permeability of the placenta to amylase was further demonstrated by Kito (1919) who injected the enzyme into pregnant guinea pigs and found that its passage to the conceptus was fairly rapid.

Since all biocatalysts tend to concentrate at the site of their activity, it is significant that, although the maternal blood contains more amylase than the foetal blood or amniotic liquor, the trophoblastic placenta contains remarkable stores of amylase, which quantity exceeds by over thirty times the diastase concentration of the maternal blood and by eight times the diastase concentration of the maternal liver (Maeda, 1924), which organ is the primary site of action for the enzyme in the maternal host. Not only does the trophoblastic placenta contain "remarkable stores of pancreatic amylase", but the excreted chorionic gonadotrophin in pregnancy urine ls always found normally with an heavy adsorption of pancreatic amylase (Nothdurft, 1944), despite the fact that the foetal (as well as the early post-natal) pancreas produces no amylase (Best & Taylor, 1943). Since adsorption to its substrate is the first step in the selective action of an enzyme, the engagement of chorionic gonadotrophin by amylase in the pregnant diabetic, then, can not possibly be as complete as in normal pregnancy; for, to the pancreatic deficit of amylase in the diabetic mother are added the imperative demands of the placenta in its "concentration" of this enzyme. Indeed, in view of the fact, then, that pancreatic amylase is highly specific, even in very low concentrations, in its digestion of chorionic gonadotrophin — and because it is a commonplace of physiology that pancreatic amylase lacks any known inhibitors in the body, being found in the active state in the serum and urine — there remains no impediment, theoretical or real, to obstruct the necessary digestion of the trophoblastic *glucoprotein,* chorionic gonadotrophin, by pancreatic amylase. The direct role of the pancreas gland in the physiology of gestation is further demonstrated by the many abortions, premature deliveries and stillbirths in rabbits made diabetic with alloxan (Miller, 1947); the condition is not ameliorated by insulin administration (Krebs, 1949).

Since the unobstructed action of pancreatic amylase on the glucoprotein of chorionic gonadotrophin does not insure, after cleavage of the carbohydrate prosthetic group, complete digestion of the protein moiety, the intervention of pancreatic proteases in the process is necessary. Unlike amylase, the pancreatic proteases — chymotrypsin, trypsin, etc. — are produced early and in considerable quantity. That the foetal pancreatic proteases are free to act here has been shown frequently during the past half century by the chemical demonstration of such enzymes in the *active* state in the foetal gut and liquors. Lysis of the chorionic gonadotrophin molecule is thus completed by the pancreatic proteases, such as chymotrypsin.

Thus despite the absence of foetal pancreatic amylase, the foetal pancreatic proteases are capable of restraining, to a degree, the proliferation of trophoblast and the excess production of chorionic gonadotrophin. The existence of antitryptic factors in the serum has long been known, and it is these factors that prevent the dramatic digestion of the trophoblast. The thesis that trophoblast overgrowth of a dangerous nature can ensue from a deficiency of maternal amylase and a relative and/or absolute deficiency in the pancreatic proteases of mother and foetus, to result in a chorionepitheliomatous overgrowth of the trophoblast — as the most malignant of all exhibitions of cancer — is indicated, in part, by the fact that numerous workers over the past half century have reported an elevation of tryptic inhibition in cancer sera — some ascribing to the phenomena diagnostic and/or prognostic utility (Brieger & Trebing, 1908; von Bergmann & Bamberg, 1908; Schultz & Chiarolanza, 1908; Herzfeld, 1908; Orszag & Barcza, 1909; Brenner, 1909; Weinberg & Mello, 1909; Torday, 1909; Schlorlemmer & Selter, 1910; Vecchi, 1911; Dynchno, 1912; Guthman & Hess, 1928; Clark, Clifton & Newton, 1948; West & Hilliard, 1949). It is of interest that all of these workers found the elevation in tryptic inhibitor in *all* exhibitions of cancer studied, and not one excluded from their generalization the most malignant of all exhibitions of cancer — chorionepithelioma. That the growth of the trophoblast is, in part, governed through the foetus, is demonstrated by Huggett & Pritchard (1945), who destroyed the definitive embryos of rats while leaving the placentae intact. With the humorally mediated tropholytic influence from the foetal circuit ablated, within a period of five days, the trophoblast grew ten fold during the period *normally characterized by pronounced trophoblast degeneration.* This, perhaps, adumbrates the frequency of toxemia in hydatidiform moles and the precedence of 50 per cent of all chorionepitheliomas (Boyd, 1946) by such moles. On the other hand, as we have already reviewed in pregnant diabetics, a non-insulin dysfunction of the maternal pancreas in humorally mediated factors (enzymes) that act in an alkaline medium (blood) is accompanied by a marked proliferation of pregnancy trophoblast, as reflected in an excess of chorionic gonadotrophin and a deficiency of syncytial steroids.

It has been suggested that, under certain conditions, the tryptic inhibitor index of the serum might be so elevated that the injection of any practical quantity of crystalline chymotrypsin would be *completely* neutralized or inactivated. That the enzyme chymotrypsin does not afford an unique or peculiar exception to the law of mass action is shown by the Harvard group (Tagnon, Weinglass & Goodpasture, 1945) who found that intravenous injection of substantially sublethal doses of chymotrypsin into dogs resulted in fibrinolysis and fibrinogenolysis *in vivo,* as reflected by the extension of the clotting time. We have found this reaction to be linear, and the fact of some *in vitro* fibrinolysis — despite the varying antitryptic indices — indicates that some chymotrypsin remains free to act, as the mass law requires. That such material is apparently without immediate or permanent toxicity in proper doses (protein sensitivity excepted) is further suggested by the fact that one of the authors, over the past four years, has experimentally taken 60 mgs of crystalline chymotrypsin intramuscularly at indefinite intervals without any untoward subjective reaction or objective sign.

The Hierarchy of Mechanisms in Pregnancy Toxemias

PRIMARY in the pathogenesis of the pregnancy toxemias is the failure of the maternal and/or foetal pancreas to produce, qualitatively and quantitatively, the adequacy of enzymes necessary for the conversion

of the gonadotrophin-producing cellular trophoblast to the syncytial steroid-producing trophoblast, which failure is reflected in the relative excess of chorionic gonadotrophin in the pregnancy toxemias.

SECONDARY to the deficit in syncytial steroids and the excess of chorionic gonadotrophin are the vasospasm of the coiled arteries of the uterine endometrium and the consequent ischemia, anoxemia, necrosis, histamine and tyramine release. Though eclampsia is possible in extra-uterine pregnancy (Pride & Rucker, 1942), normally the uterus participates in the phenomenon. Menstruation has been described as the result of the steroid deprivation of the endometrium, mediated by reciprocal ovarian-pituitary inhibition; and we have suggested that birth is an epimenstrual phenomenon due to steroid deprivation, as the result of the loss of hormone support, through the ablation of the hormone-producing trophoblast. In his monumental work in the observation of the physiology of menstruation in intraocular endometrial implants in the Rhesus monkey, Markee (1940) found that endometrial bleeding and necrosis follow the vasoconstriction of the sphincters of the coiled arteries as a result of the physiological withdrawal of steroid support. This same phenomenon can be induced experimentally or clinically through surgical or chemical castration. In the premature deprivation of the endometrium of steroidal support during the span of gestation, phenomena that would be expressed in normal menstruation or birth are expressed in syndrome of the pregnancy toxemias.

TERTIARY to the premature involution of the endometrium are the release of the necrotizing toxins from the uterine tissue. The toxicity of the menstrual discharge is a fact lost in the antiquity of folkways. The Smiths (1948) are notable among those who have experimentally defined the analogy of the menstrual toxins with those arising in pregnancy toxemia. The identification of the tertiary phenomenon with a steroid deficit (*secondary* phenomenon) or endocrine imbalance, is seen in the immediacy with which the far flung effects of the necrotizing toxins are often resolved by correcting the estrogen deficit through the administration of estrogen (Bowen, 1944; Smith, 1948).

Were progesterone alone capable of maintaining the gestational integrity of the uterus, toxemias characterized by an excess of chorionic gonadotrophin, as a result of the overgrowth of cellular trophoblast, would never occur: chorionic gonadotrophin itself acts upon the the corpus luteum to stimulate the output of progesterone. In fact, in hydatidiform moles, bilateral luteal cysts with a prodigious output of progesterone are not infrequently seen—*even in the presence of eclampsia.* (The luteal cyst, of course, follows from the excessive stimulation of the corpus luteum by the increased quantity of cytotrophoblastic gonadotrophin arising from the trophoblast cells of the mole). Thus we see the rationale of Alexander Symeonidis' (1949) recent report from the National Cancer Institute that the injection of progesterone into rats late in pregnancy caused "symptoms" and tissue changes strikingly similar to those found in human eclampsia. While Symeonidis observed the results of the direct injection of progesterone, Snyder (1942; 1943) obtained fundamentally the same phenomena through the injection of chorionic gonadotrophin, which, of course, stimulates the production of progesterone from the corpora lutea of the ovary. The anatomic evidence of uteroplacental apoplexy in rabbits obtained by Snyder through the injection of chorionic gonadotrophin showed that the injury attained the magnitude of general systemic changes or intoxication, resulting in death.

The cogency of estrogen therapy (e.g., diethylstilbestrol) is illuminated in the fact that estrogen, by inhibiting the gonadotrophin-producing cytotrophoblast, decreases the stimulus to the progesterone-producing corpus luteum, with a consequent decrease in progesterone and an increase in syncytial steroids following from the newly produced syncytial adaptation of cellular trophoblast. This was seen by Adair and others when the administration of sex steroids in pregnant women was found so to inhibit the gonadotrophin-producing cytotrophoblast that their urines became negative with the Ascheim Zondek reaction. The amenability of the cellular trophoblast of chorionepithelioma in the same fashion was strikingly demonstrated by Kullander (1948) who found that the administration of stilbesterol resulted in a clinical improvement that paralleled the decline in the secretion of chorionic gonadotrophin. Of course, the prognostic utility of this index in chorionepithelioma is commonplace. Though Kullander did not cure his patients, so long as stilbesterol controlled the secretion of chorionic gonadotrophin, they improved. Regression in the clinical state with an increase in gonadotrophin secretion was found to follow repeatedly on the discontinuance of stilbesterol—with a decrease in hormone secretion and clinical improvement following the reinstitution of hormone therapy.*

QUARTERNARY phenomena in the toxemic state do not proceed mechanistically from the tertiary mechanism of necrotoxin release, but rather chiefly from the interrelatedness of tertiary and secondary phenomena. We may include among the quarternary phenomena the following: fluid imbalance, salt retention, uremia, glomerular degeneration, hepatitis, and placental infarction. Since the effects of an excess of chorionic gonadotrophin are far-reaching, the thesis that attributes salt retention (or potassium-sodium imbalance) to adrenocortical dysfunction is

* To those who, like the authors, accept the unitarian or trophoblastic thesis of cancer (Krebs, 1946; Krebs & Gurchot, 1947; Gurchot, Krebs & Krebs, 1947; Krebs, 1947) in which the most malignant of all exhibitions of cancer — chorionepithelioma — epitomize the nature and origin of exhibitions of lesser malignancy, the findings of Kullander appear to bear particular pertinency. They explain, perhaps, the undeniable palliative effects, under certain conditions, of estrogen in prostatic carcinoma and secondary bone growths; and testosterone in mammary growths; the cellular trophoblast depressing function is itself constant for androgen and estrogens, but the use of the physiologically antagonistic steroid serves also to induce atrophy of the somatic elements in the tissue physiologically capable of localizing steroids. The ineffectiveness, then, of the same steroids in *all* malignant exhibitions would be accounted for by the physiological lack of the ability of the functional somatic elements in the tumor to localize such steroids in effective concentrations.

especially tenable, in view of the fact that the effects of the trophoblastic hormones on the anterior pituitary extend to the adrenocorticotrophic hormones that account for the increased production in pregnancy of such steroids as the presently publicized Cortisone. Uremia is, in part, consequent upon glomerular degeneration that proceeds from the necrotizing toxic amines arising in response to the endometrial necrosis which proceeds from the deficit in syncytial steroids, conditoned by an inadequacy in pancreatic enzymes. That the *primary* phenomenon of enzyme inadequacy may extend *directly* to some quarternary phenomena is possibly suggested in the action of trypsin inhibitor in preventing the toxic effects of human placental thromboplastin (Fulton & Page, 1948).

Finally, the mechanical impairment of the syncytial membrane, expressed in the inadequate conversion of cellular trophoblast, can not be overlooked in the quarternary phenomena. Indeed, only a brief glance at the normal syncytial trophoblast tells us that it must perform a task more complicated than that of the kidneys in transferring maternal-borne nutrition to the foetus and removing the excretory products. This too little-studied semipermeable membrane not only carries on excretory functions analogous to those of the kidneys, but in addition to this it acts as the sole nutritional membrane to the foetus; it also serves in the capacity of a respiratory membrane with a two-way diffusion of gases; it selectively permits the escape of protein molecules as large as those of insulin—35,000 m.w.—and excludes the passage of other molecules of the same size; it admits certain immune globulins through its membranes and it excludes others; it selectively excludes bacteria, rickettsia, and most viruses; and it controls the endocrine balance to a large extent.

It is little wonder, then, that the impairment of the morphological integrity of this critical membrane, through failure in the provision of an adequate constituent syncytium, will be felt throughout the host in a profound upset in the organs of detoxification and excretion. To impair the functional integrity of the syncytial membrane is, certainly, tantamount to excluding the foetus from adequate renal function *both foetally and maternally.* Hypertension is a logical corollary of such a pathological process. The wonder is not that the signs and symptoms of this basic impairment in the trophoblast, buttressed by associated pathogenic mechanisms, are reflected as widely and dramatically as they are throughout the maternal (and foetal) soma, but that their repercussions are not even more spectacular.

Conclusion

There is no longer any justification for the appellation of the pregnancy toxemias as a pathological state comprising "the disease of theories". Not only was the pathogenesis of the pregnancy toxemias as obscure as that of cancer, but the solution of the problem of pregnancy toxemias is found implicit in the solution of the cancer problem itself. This solution is defined in the unitarian or trophoblastic thesis of cancer.

The pregnancy toxemias are characterized by an inadequacy in the concentration of pancreatic enzymes in the blood of the maternal host. This inadequacy is responsible for the overgrowth of the cellular trophoblast (cytotrophoblast), and this overgrowth is reflected in the abnormally high titer of chorionic gonadotrophin found in the blood and urine in toxemic pregnancies. The syncytial deficit is the result of the failure in the conversion of the cellular trophoblast to the syncytial state. This accounts for the excess of chorionic gonadotrophin *and the marked deficiency in syncytial steroids that typify the pregnancy toxemias.* The far-reaching and dramatic signs and symptoms present in the various toxemic states are all primarily an expression of the enzymatic phenomena involved in the original impairment of the syncytial (placental) membrane.

Because *in vitro* studies have clearly shown that the crystalline pancreatic enzymes — chymotrypsin, pancreatic amylase and carboxypeptidase—will *selectively* digest the chief protein of the trophoblast cell, and do so in a concentration and at a pH and temperature that are readily tolerable *in vivo,* it is recommended that the specified crystalline enzymes of the pancreas be so employed as to restore the enzyme status physiological to pregnancy.

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ACUTE APPENDICITIS COMPLICATING PREGNANCY

WILLIAM SIDNEY GOLDFARB, M.S., M.D. New York, N. Y.

Acute appendicitis is a serious complication of pregnancy since it not only threatens the life of the mother, but the unborn child as well. The overall incidence of pregnancy complicated by appendicitis varies from author to author. Cosgrove in 1937 reported a ratio of one case in every 1,380 deliveries at Margaret Hague Hospital, while Mussey and Crane of the Mayo Clinic gave the incidence as two per cent. Johnson believes that the incidence of acute appendicitis in women was the same whether they were pregnant or not, and it was Findley's contention that 70 per cent of women who have had attacks of appendicitis which subsided and were not operated upon will have this recur during their following pregnancies. Crossen reports that 80 per cent of all cases of acute appendicitis in pregnancy occur in the first six months of pregnancy.

Meiling believes that it is unlikely that any one observer will personally see or attend very many of these cases, though Norton and Connell have succeeded in collecting from the literature and hospitals available to them 1,110 cases of appendicitis in pregnancy. Of these, nine occurred in labor or the puerperium. Meiling in 1947 reported a series of 26 cases of appendicitis in pregnancy in a 13 year survey of the services of the University Hospitals of Cleveland. During this time, there were 49,681 deliveries, or an incidence of one case in 1,910 deliveries. In this series, 84.6 per cent were in the first six months of pregnancy.

DIAGNOSIS

In 1905 Fueth described the anatomical displacement of the cecum and appendix during pregnancy. Upward and lateral displacement from its normal location in the false pelvis usually begins at the end of the third month of pregnancy, so that the appendix at the end of the sixth month is out of the false pelvis and in the abdomen proper. The non-pregnant location of the appendix is resumed between the tenth and twelfth day postpartum. The displacement alters the signs of maximum tenderness over the McBurney point, muscle rigidity, rebound tenderness, psoas spasm, and the tenderness found on rectal examination in the iliac fossa.

To make the clinical picture of acute appendicitis still more difficult, the signs and laboratory findings are altered by the presence of the pregnancy. Carey and Litzenberg report the white blood count in pregnancy to be between 8,700 and 10,000, rarely over 12,500. During labor, Baer reports the leucocytosis averages 18,000, and may be as high as 32,000. Acute appendicitis, according to Homans, is usually associated with a leucocytosis between 10,000 and 20,000. A figure closely approximated in normal pregnancy.

Titus believes that a rapid blood sedimentation rate indicates infection. By use of Linsenmeyer's tube, Titus gives the average normal rate of approximately one hour for the sedimentation of red corpuscles to the 18 mm. mark. In contrast to this, Vogt reports an increase in the blood sedimentation rate during pregnancy normally, going as high as 23 mm. per hour and reaching 32 mm. per hour in the ninth month, and returning to normal six weeks post-partum. Also, various gynecological, obstetrical and genito-urinary complications of pregnancy, such as pyelitis, cholecystitis, abruptio placenta, and "red" degeneration of uterine fibroids must be differentiated from acute appendicitis.

PROGNOSIS

The seriousness of this complication is further shown by maternal mortality statistics. According to McDonald, when the disease is limited to the appendix, the maternal mortality rate is 0.71 per cent, and rises as high as 30 per cent when peritonitis develops. This same author states that the incidence of abortion in pregnancy with appendicitis is 11.4 per cent if the process is limited to the appendix, going as high as 72 per cent in a generalized peritonitis. Jerlov reports rates of similar magnitude for abortions in pregnancy with appendicitis. Meiling found that the fetal and neonatal mortality was 34.6 per cent and that the maternal mortality rate was 7.69 per cent with the incidence of abortions 26.1 per cent.

Meiling states that the maternal mortality rates are greatest in patients who abort. Yet Maes and Boyce believe that patients abort because they are dying, they do not die as a result of aborting. Greenhill reports that 50 per cent of patients abort subsequent to perforation of the appendix, and this produces an increase of five per cent in the maternal mortality. Irving gives the maternal mortality rate as 11.8 per cent, and stated 23.5 per cent either abort or go into premature labor after appendectomy.

TREATMENT

There are several advocated methods of treat-

ment. Zander in 1942 said, "The pregnant woman with acute appendicitis is first a surgical problem and second an obstetrical problem. Operation should be carried out without delay and delivery accomplished by natural channels at term unless an absolute indication is present demanding abdominal section." Cosgrove in addition to stressing the need for early operation, cautions against combining any manipulation to terminate the pregnancy with this surgical treatment.

Marbury gives a different opinion. Though Marbury suggests that the appendix may be simply removed, he goes on to further say, "If abortion occurs the change in the size of the uterus breaks up what protective adhesions have formed and allows the peritonitis to become generalized. Consequently, it may be wiser to make a paramedian incision and empty the uterus by cesarean section first and deal with the appendix secondarily. Where generalized peritonitis is revealed at the time of exploration, infection of the endometrium is inevitable, therefore a Porro cesarean section should be done."

Greenhill states, 'When one considers the high mortality of suppurative peritonitis at or near term, perhaps it would be best in the interests of the two individuals to remove the appendix and to do a Porro cesarean section at the same time. Not enough cases are on record to definitely settle this point, but the classic cesarean section is contraindicated. Laparotrachelotomy is safer, but the extraperitoneal section is still better."

With the advent of chemotherapy and antibiotics, another era has appeared in both surgery and medicine. Surgical procedures that would never have been attempted heretofore, are now being performed with safety. So that at present, we may look forward to fewer hysterectomies hysterotomies in the surgical treatment of this complication of pregnancy, when the treatment includes appropriate chemotherapy and antibiotics.

Case Report

The following case report is cited to illustrate some of the points mentioned above.

Twenty-six year old, white, nulliparous, married female became acutely ill at 2:00 A. M. of October 6, 1946. She was awakened by severe abdominal pain present in both lower quadrants, which kept her awake all night. Nausea was present. Patient was seen by me at 12:30 P. M. that day and immediately hospitalized.

Past history irrelevant except for occasional episodes of right lower quadrant tenderness since February, 1946. Patient has been amenorrheic since April 22, 1946, and registered for prenatal care in July. The diagnosis of pregnancy was confirmed by the presence of a soft, eight to ten weeks' size uterus. The right ovary was enlarged to about four by six cm., firm moveable and somewhat tender. Left adnexa was negative. The prenatal course had been uneventful at the time of the acute episode, except for occasionally finding slight tenderness in both lower quadrants of the abdomen on examination.

On admission to the hospital, her temperature was 100.4 degrees F., blood pressure 106/60, and pulse 70 per minute. Examination was essentially irrelevant except for the abdomen which had tenderness and rebound tenderness in the right lower quadrant, to the right of the umbilicus, and radiating to the right lumbar region. No rigidity was present. Uterus was soft, non-tender, and six plus months gestation in size. No costo-vertebral tenderness was found. Adnexal findings were the same as previously described. Haemoglobin 80 per cent (Sahli), W. B. C. 26,600, P. equals 90 per cent, and L. equals 10 per cent. Blood sedimentation rate was 14 mm. in one hour.

Having excluded a genitourinary condition with intravenous pyelography (principally to rule out ureteral obstruction), the diagnosis of a probable appendicitis was established clinically and laparotomy performed. On opening the peritoneal cavity, there was about fifty cubic centimeters of yellow fluid. The appendix was found recessed behind the uterus on the right. It was indurated, ligneous, acutely inflamed and surrounded by fibrinous deposits. An appendectomy with drainage was done. Histological examination confirmed the gross description of an acute inflammatory process of the appendix.

Post-operative course was stormy due to marked distention. Treatment consisted of sedation, sulfadiazene (Grams ii at onset and Gram i every four hours), penicillin (30,000 units every three hours), intravenous fluids, and Wangensteen drainage. The highest temperature was 102 degrees F. on the second day and then rose to that on the fourth day again. Drainage through the abdominal wound was profuse the first few days. Culture from the wound revealed B. coli and Bacillus proteus vulgaris. Smears showed gram negative bacilli. Later the discharge became a sanguino-purulent, foul material at the site of the drain, while the rest of the incision was healed by primary union.

Prophylactically ephenyl acetate 50 mgm. twice a day and proluton five mgm. twice a day were given to avoid the onset of premature labor. No pituitrin was used to counteract distention, because of the possible effect on the uterus. However, painful intermittant uterine contractions appeared on the fifth post-operative day. A bulging of the cervix occurred with each uterine contraction. She was given morphine sulphate gr. one-quarter intramuscularly, and the contractions ceased.

The drain was loosened gradually and finally removed on the tenth day post-operative. Chemotherapy and antibiotics were used up to the ninth and tenth days post-operative, respectively. Patient was out of bed on the eleventh day and sent home on the thirteenth day post-operative. The wound was completely dry for the first time on December 5, 1946. The remainder of her prenatal course progressed uneventfully, and on January 7, 1947, she was delivered spontaneously of a normal living female child of five pounds four ounces.

Summary

The incidence of acute appendicitis in pregnancy is discussed and the difficulties in making this diagnosis is presented. Both the treatment and

prognosis of this complication are reviewed. A case report of a six and one-half month gestation complicated by acute appendicitis is quoted.

I wish to acknowledge, with appreciation, the assistance of Abraham B. Tamis, M.D., F.A.C.S., in the preparation of this presentation.

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A THEORY ON THE ACTION OF CORTISONE

A. D. JONES, M. D. New York 58, N. Y.

The onset of rheumatoid arthritis following severe emotional upsets and the reversibility in the wake of violent rage reactions leads one to the assumption that the causative factor behind this ailment lies in an emotional dysfunction. Emotional reactions in response to stimuli, painful or pleasant, are converted into centrifugal nerve impulses in certain areas of the brain of which the thalamus and the hypothalamus may represent the more important but not the sole centers. The impulses reach the effector organs either directly via the peripheral nervous system or indirectly through stimulation of endocrine organs or cells capable of producing chemical products of a catalytic nature. A Theory on the Action of Cortisone—Con't.—— Faulty functioning of organs traceable to their innervations resulting eventually in organic changes are caused by endlessly repetitive stimuli usually arising in the individuals immediate environment. Patients afflicted with rheumatoid arthritis are sensitive individuals incapable of dealing adequately with hostile feelings. Rather than let go they stiffen up. When hurt or insulted they keep their hand in the pockets and make a fist which no one can see. This is to be taken both literally and figuratively. The continuous muscular contractions will press the cartilaginous surfaces against each other resulting gradually in a pressure atrophy. Also the intense contraction will squeeze the blood out of the tissues thus keeping them in a state of undernutrition and anoxemia. Eventually a modified degeneration and limited reparative processes of the surrounding connective tissues take place.

The most remarkable therapeutic effect of cortisone lies in the functional improvement of the joints regardless of the extent of pathological changes. This can only mean whatever lesions can be found surrounding the articulations are only secondary to an agent which must have an extra-articular origin. Eliminating this agent restitutes the joint to normal or near normal function. This is in line with the statements above. One of the striking side effects of cortisone is the improvement in the emotional tone which the authors Boland and Headley (Boland, E. W. and Headley, N. E., "Effects of cortisone acetate on rheumatoid arthritis, *J. A. M. A.*, Oct. 1, 1949) feel to be greater than one would expect from an improvement of the rheumatoid disease alone. Therefore the conclusion seems to point to a faulty emotional response mechanism creating a state of muscular tension capable of being inhibited by the action of cortisone. The question arises at what level? The change in feeling tone amounting in one patient to a state of hypomania indicates the involvement of the emotional centers. In other words, cortisone is capable of effecting a change in the emotional reactions irrespective of the continuing presence of a faulty response pattern within the patient. This may be compared with the temporary changes induced through the administration of intoxicating or stupefacient drugs. It would be interesting to study the effect of cortisone on the various psychoneuroses and psychoses.

BOOK REVIEWS

STUDIES IN PEDIATRICS AND MEDICAL HISTORY, by Abraham Levinson, edited by Dr. Solomon R. Kagan, published by Froben Press, Inc., 1949.

The friends and colleagues of Dr. Abraham Levinson did not wish to wait until he had reached the proverbial "three score and ten" to express their esteem and affection for him in a tangible way. They are presenting this Anniversary Volume to him on his sixtieth birthday in recognition of his signal achievement as physician, teacher, author and research worker.

The contributions contained within these pages were written by men of international reputation. They cover many significant advances in pediatrics, pediatric neuropsychiatry and medical history—Dr. Levinson's special fields of endeavor.

NEW WAYS IN DISCIPLINE (You and Your Child Today), by Dorothy Walter Baruch, published by Whittlesey House, McGraw-Hill Book Company, Inc., 1949.

On the shoulders of parents and teachers falls the major task of imparting to children the ways of our difficult culture. It is their privilege and their responsibility to make civilized people out of little hellions and little angels alike. The parent starts the child out in life. Later, parent and teacher share the task. Too often, the sharing is in name only. The parent goes one way, the teacher another. Even in their psychological orientation, they are miles apart. This makes obvious difficulties for the child. Parents and teachers need not only to know each other but to pool knowledge and information. Even more important, they need to have some common, basic understandings of the psychological aspects governing wholesome discipline today.

When a child first goes to school, he takes with him all the years that have gone before. Into kindergarten, he takes his infancy and his toddling days. When he enters high school, he carries within all the experiences he has had in other grades as well as at home. And so, the teacher and the parent both should know something of the years that have gone before. They should know of the child's emotional needs and requirements and of the kind of regimen which would have furthered his best adjustments at each period of his life. For, with such common backgrounds, teachers and parents together can make up in the present for mistakes that have occurred in the past. With such common backgrounds the various adults can pool effort and skills to make the future a happier one for both them and the child.

One other person enters the scene all along. This is the doctor. Parents look to him for help and advice. Teachers similarly go to him as a source of wisdom. Therefore, it will be beneficial if he, too, can acquire similar orientation and insights into the psychological management of children to add to his store of knowledge on the physical side.

It is to these three groups of people—parents teachers and doctors—that the present book is addressed in the hope that it may bring to them some of the answers they are seeking in helping children acquire new strengths to meet a new world.

DISEASES OF THE HEART, by Charles K. Friedberg, M.D., published by W. B. Saunders Company, 1949.

The swift pace of recent advances in heart diseases calls for a reorientation in presentation and a modification in emphasis from that found in available standard works on cardiac disease. In particular, special emphasis on the pathologic physiology of cardiac disorders, including the pathogenesis or mechanism of the symptoms and signs of circulatory failure of angina pectoris and myocardial infarction and of the various manifestations of the individual cardiac disease. The increased utilization of quantitative measurements in the clinical study of circulatory disease is reflected in detailed discussion of the cardiac output, blood volume and extracellular volume, peripheral and intracardiac blood oxygen concentration and intracardiac pressures, body fluid and tissue electrolytes and renal and pulmonary blood flow. Throughout the book these measurements are applied to clinical understanding and practical usage in the everyday diagnosis and treatment of cardiac disease.

Roentgenology and electrocardiography have become essential elements of cardiologic practice and are thoroughly discussed. Individual chapters devoted exclusively to a formal presentation of electrocardiography and roentgenology have been omitted. Instead, emphasis has been placed on the application of electrocardiographic and roentgenologic interpretations to clinical practice, in which these findings must be integrated with the clinical history, symptomatology and other objective data.

Electrocardiography has been discussed in detail in connection with the arrhythmias, angina pectoris, myocardial infarction, pericarditis and myocardial disease, while both electrocardiography and roentgenology, including angiocardiography, have been amply considered in connection with such subjects as chamber enlargement, valvular heart disease and congenital cardiac lesions. To a lesser extent electrocardiographic and roentgenologic findings are also described in connection with almost every other type of heart disease, according to the importance and diagnostic value of these findings relative to other clinical features. A number of other graphic methods, including phonocardiography, roentgenkymography, electrokymography (fluorocardiography) and endocardial electrocardiography, have recently received increasing attention from cardiac investigators and these have been briefly mentioned when pertinent. An excellent evaluation of the current concepts of heart disease at every age level.

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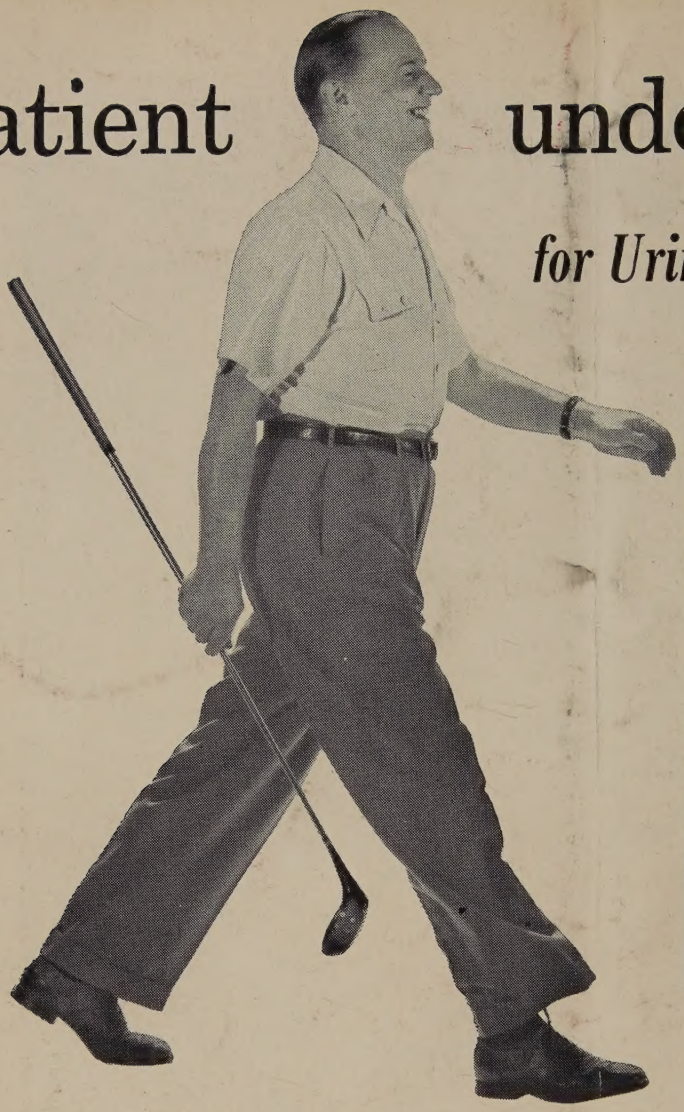

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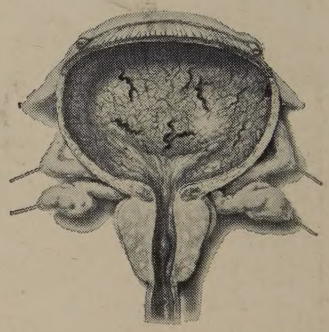
SYMPTOMS



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